FRESH AIR '97'

A LOOK AT FDA'S MEDICAL GAS REQUIREMENTS

I would like to thank you for giving me this opportunity to speak to you today on a very important subject, compressed medical gases (CMG) and FDA's requirements for the manufacture of medical gases.

Before we get started, medical gases are considered drugs and are required to be dispensed by prescription only, except medical oxygen used for emergency resuscitation. Medical gases not filled in accordance with the current good manufacturing practice (GMPs) regulations can and have resulted in medical gases that are contaminated which can cause serious injury and/or death to patients administered the gas. In fact, injury and death of patients has occurred in the past due to GMP problems.

Who exactly is required to register with the FDA? Any person or firm filling liquid to liquid, liquid to gas, and/or gas to gas is considered a manufacturer and as such is required to register and list with the Agency and to comply with the GMPs.

One type of operation not required to register is a distributor. This is a firm that receives fully labeled, finished drug product either liquid in large cryogenic vessels, i.e., VGLs/GPs, etc. and/or high pressure cylinders and does not manipulate the product nor the labeling in anyway. A distributor should establish and follow recall, complaint and distribution procedures capable of determining the traceability of the drug product. Please note that this type of operation does not pertain to cryogenic home vessels.

In addition, we are unaware of any schools of pharmacy or State Boards that offer education and/or training for the filling of CMG, therefore, any pharmacy involved in the manufacturing of medical gases would be required to register and list with the Agency and will be inspected. However, a hospital pharmacy that provides oxygen for inpatient use only would not be required to register.

Presented by Duane Sylvia, Consumer Safety Officer, Center for Drug Evaluation and Research, Office of Compliance during the CASA/FDA Medical Gas GMP Workshop held April 22, 1997 at Arlington, Virginia.

What are the good manufacturing practices for medical gases? Unfortunately, there are no specific regulations for medical gases. In the preamble of the revised CGMP regulations issued September 29, 1978, the agency recognized that medical gases were quite different from the traditional dosage forms in many respects. However, the Commissioner stated that the requirements in the more general CGMP regulations, with certain stated exceptions, are applicable.

So based on the information gathered from 17 years of inspections of compressed medical gas firms and several meetings with the Compressed Gas Association (CGA), the first CMG guideline was issued in June of 1981, with a subsequent revision in 1983. In February of 1989 the Compressed Medical Gases Guideline was revised to address the home respiratory care area, or the delivery of liquid oxygen to patients at home. At the present time, we are working with the CGA on updating the 1989 guideline. The information addressed in this presentation will be the basis for the new guidance document.

Let's briefly look at how FDA enforces the requirements and what our experience has been with the medical gases industry from a national standpoint.

FDA has the responsibility of enforcing the Federal Food, Drug, and Cosmetic Act (the Act). This law gives FDA the authority to conduct inspections, collect and analyze product samples to assure that foods, drugs, cosmetics, and medical devices are safe and meet the appropriate quality standards.

The Act states that a drug, such as medical oxygen, is adulterated and subject to legal action if it is not manufactured in accordance with the GMPs, or does not comply with appropriate official standards such as strength and quality.

According to the Act (Section 501) a drug is deemed adulterated if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practices to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

Section 510 of the Act requires all drug manufacturers, including fillers of medical gases, to REGISTER ANNUALLY with the Agency and to inform FDA of the products produced. Failure to comply with this requirement is a violation of the law which can ultimately result in legal action.

Finally, Section 704 of the Act authorizes FDA to enter each facility to conduct an INSPECTION to assess compliance with the law. Failure to permit an inspection is a violation of the law, which can eventuate in legal action. In December 1996, the Baltimore District was refused inspection by a medical gas firm. On December 15, we conducted the inspection under a court order accompanied by the U.S. Marshals. We

also took regulatory action against the firm based in part on the refusal and significant GMP problems.

FDA is required by statute to inspect each registered drug facility at least once every two years. Often, it is more frequently, especially where we suspect or know of a problem with a specific firm or the industry as a whole.

If the inspection determines that a firm is significantly deviating from GMPs and satisfactory corrections have not been initiated, FDA will initiate regulatory action intended to prompt the firm to correct its problems and protect the patient.

There are several courses of action we can take within the authority of the law, these are: a Warning letter; Seizure of the Product including storage tanks, high pressure cylinders, cryogenic home vessels on the premises, and trucks/vans containing the large cryogenic vessels; an Injunction; a Prosecution; Disapproval of government contracts; and informing the Health Care Finance Administration.

What's the general state of compliance in the compressed medical gases industry today? We are finding that the general state of GMP compliance is not as high as we would like. This is quit evident by the data contained in this slide which represents the total number of regulatory actions for the fiscal years of 1992 to 1995. In '92' - 112; in '93' - 117; in '94' - 91; in '95'- 109, and in '96' - 103. The next slide shows the seizure actions approved, 21 in '92', 12 in '93', 15 in '94', 11 in '95', and 6 in '96'.

Although, we see some improvement, this regulatory action rate indicates a need for the industry to improve its overall compliance with the GMPs.

DEFINITIONS

1) Large cryogenic vessels/Dewars which contain the incoming drug product, may be permanently mounted in a vehicle, such as HL119s, MDX 60s, 80s, 119s, etc., or may be portable such as VGLs (Vertical Gas Liquid), GPs (Gas Pack), or PLCs (Portable Liquid Container).

2) Storage Tank is a large cryogenic stationary holding tank with a capacity of several thousand gallons/liters of a liquid product. These are always located on the outside a facility.

3) Cryogenic home vessels (CHV) are vessels designed to hold liquid oxygen at a patient's home.

4) Cascading - This is a cylinder filling system consisting of several large sized cylinders, such as H or K-sized cylinders as the supply source or commonly referred to as a "Bank" and a filling manifold capable of filling smaller cylinders, usually D or E cylinders, either one at a time or multiple cylinders. The first supply cylinder's

valve is opened and the gas flows into the smaller cylinder(s) until equilibrium is reached. When this occurs, the first cylinder's valve will be closed and the second supply cylinder's valve will be opened allowing the gas to flow into the smaller cylinder(s). This continues until the smaller cylinder(s) is filled.

5) An uninterrupted filling sequence is a single, continuous filling sequence with no breaks or shut-downs occurring during the filling and provided the same personnel, equipment, and lot of component are used. If the filling sequence is interrupted then additional testing is required. This procedure pertains to high pressure cylinders that are filled individually, i.e., one at a time. Cylinders that are filled on a multiple outlet manifold or rack should be tested according to the requirements listed under 211.165(a).

6) The United States Pharmacopeia 23 (U.S.P.) is a reference of a select list of medicines. Included in each monograph are the standards for determining the identity, strength, quality, and purity of the articles.

LIQUID TO LIQUID FILLING
(The filling of cryogenic home vessels)

Each firm is required to adequately determine the identity and strength of:

1) the incoming liquid Oxygen U.S.P., and/or

2) the liquid Oxygen U.S.P. delivered to the customer.

Testing should be by appropriate methods to determine conformance with official specifications.

1. TESTING OF THE INCOMING LIQUID OXYGEN

If a firm dispenses liquid oxygen (LOX) from large cryogenic vessels into cryogenic home vessels, then:

a) No testing is required, as long as the receiving firm witnesses the testing, i.e., identity and strength, of each cryogenic vessel, receives a valid certificate of analysis (COA) for each vessel, and documents that the testing has been witnessed. Further, the person witnessing the testing is required to receive training specific to the analytical methodology being witnessed, and this training should be documented.

b) If the testing is not witnessed, then the receiving firm can rely on a valid COA for the strength determination, however, it should perform an identity test on

EACH cryogenic vessel received or filled by the supplier. The firm is also required to periodically verify the reliability of the supplier's analysis. This should be performed at least once a year by:

1) performing a supplier audit as outlined under Section 211.84(d)(2), Components, or

2) the firm may take a sample from a delivery to a third party for analysis for conformance with U.S.P. specifications.

c) If a firm neither witnesses the testing nor receives a valid COA, then full U.S.P. testing is required for each large cryogenic vessel received.

In addition, a firm is required to have on file the method of manufacture for the oxygen it fills in order to be exempt from the testing requirements for carbon dioxide and carbon monoxide impurities as listed in the U.S.P.

2. Testing of a Storage tank

If a firm owns or leases a storage tank, then an identity and strength test taken directly from the storage tank after each oxygen delivery should be performed before any cryogenic vessels including cryogenic home vessels are filled. Large cryogenic vessels filled from this storage tank need not be tested if:

a) No other storage tank(s) is located on the premises;

b) They are dedicated to the delivery of oxygen by the firm for home care use only; and

c) They have not been completely emptied or have not been out of service.

3. TESTING OF CRYOGENIC HOME VESSELS

The most significant condition in the filling of cryogenic home vessels is the control of the cryogenic home vessels. If the possibility exists that a contaminant or a foreign product could be introduced into the cryogenic home vessel, then the GMPs require full U.S.P. testing of each vessel. Industry practice calls for the firm that owns the cryogenic home vessels to perform the filling and to not allow any other firm to fill these vessels.

1) No testing of the CHV is required as long as the following three criteria are met:

a) Liquid oxygen is the only liquid being filled on the premises

b) Incoming liquid oxygen is adequately tested according to one of the methods outlined under the TESTING OF THE INCOMING LIQUID OXYGEN (See above),

and

c) Cryogenic home vessels are filled by the firm.

2) If any other liquid is being filled on site or if the incoming liquid oxygen is not tested in accordance with one of the methods outlined under the TESTING OF THE INCOMING LIQUID OXYGEN, then ALL cryogenic home vessels filled are required to be tested for full U.S.P. specifications.

3) If a home care company (HCC) allows their cryogenic home vessels to be filled by a third party, then the home care company is required to perform full U.S.P. testing on each returned vessel prior to release to the patient.

This concludes the testing requirements for the filling of cryogenic home vessels that are either filled on site and delivered to a patient's home, i.e., milk canning, etc. or are filled at a patient's home, i.e., curbside.

Combining a new bulk shipment of a component into a bulk storage tank with the remainder of a previously received, tested, and approved component lot causes the commingling of the material. The result is that the previously approved material becomes an integral part of an unapproved new lot and cannot be used until such lot is approved for use.

LIQUID TO GAS and FILLING LARGE CRYOGENIC VESSEL

The filling of high pressure cylinders via a liquid pump and vaporizer and the filling of large cryogenic vessels. The testing requirement for a storage tank where the product is used to fill high pressure cylinders and/or large cryogenic vessels is immediately after each delivery, the commingled liquid oxygen is tested for full U.S.P. specifications, prior to the filling of any large cryogenic vessels. This may be accomplished by:

1) taking a sample directly from the storage tank. Once commingling occurs you have a new batch, or

2) testing a cylinder from the first filling sequence (manifold or rack). This is the most commonly seen procedure.

This testing gives assurance that the commingled component or bulk is acceptable, although, finished product testing of the high pressure cylinders is still required. A storage tank is only required to be tested prior to the filling of medical product.

Once a storage tank has been tested and is acceptable for use, large cryogenic vessels, i.e., VGLs, GPs, PLCs, etc. may be filled. However, EACH large cryogenic vessel filled

is required to be tested prior to release, since cryogenic vessels usually contain residual and a commingling of new and old product results. This commingling produces a new batch which is required to be analyzed and assigned a new lot number.

Next, let's look at the specific GMPs that a manufacturer of medical gases is expected to follow. A word of CAUTION, please check the accuracy of any information you may receive with the FDA before changing or implementing a possible violative GMP practice or procedure.

RESPONSIBILITY OF QUALITY CONTROL UNIT
Section 211.22(a)

Each firm is required to establish a quality control unit (QCU) that has the responsibility and authority to approve or reject all drug product containers, closures, in-process materials, packaging material, labeling, written procedures, the authority to review production records to assure completeness and accuracy, and is responsible for the approval or rejection of all manufactured drug product. The responsibilities and procedures applicable to the QCU should be in writing and these procedures should be followed. For smaller firms, it would be acceptable to designate a single individual with the above responsibilities.

PERSONNEL QUALIFICATIONS
Section 211.25(a)

In any field of human endeavor there are hazards which may be created by preoccupation, mental lapse, carelessness and the like. Therefore, all training needs to revisited at frequent intervals and needs to be conducted by a qualified individual.

A firm is expected to establish detailed written procedures (training program) outlining the specific areas of the firm’s operation to be covered. On-the-job training is acceptable, as long as the training is conducted by a qualified individual on a frequent basis.

The lack of GMP training is one of the most overlooked areas observed at medical gas firms. GMP training should be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with the GMP requirements that are applicable to each operation.

1) For additional information, I recommend contacting the Compressed Gas Association located in Arlington, Virginia at (703)412-0900. The CGA develops standards for the industry and has numerous educational pamphlets and videos that address all aspects of the manufacturing of both industrial gases as well as medical gases.

2) Another good tool to assist a firm that fills high pressure cylinders is the Compressed Medical Gases - CGMP Inspection videotape, available from the National Technical Information Service, (703)487-4660. Request AVA19784VNB1. This videotape is a good training film covering the filling of high pressure cylinders only.

3) The FDA now has a compressed medical gases web page where you can review and retrieve: 1) the quarterly publication entitled The Human Drug CGMP Notes that address policy questions and other pressing issue under the GAS WHAT? column, 2) the February 1989 compressed medical gases guideline, and 3) the Fresh Air 97 presentation. To obtain an electronic version of these documents and previous editions, using Internet type http://www.fda.gov/cder/gases.htm.

4) Check with your supplier who may offer GMP training and other types of training for their consignees through out the year.

One of the most overlooked areas of training for the filling of liquid to liquid is the firm's employee responsible for witnessing the testing of the incoming product. The employee may receive training from the supplier on the analytical methodology used by the supplier with special attention on the calibration of the equipment.

All of the above training requirements should be document.

DESIGN AND CONSTRUCTION
Section 211.42

Any building used in the manufacture, processing, or holding of a medical gas should be of suitable size and design. There should be adequate space for the orderly placement of equipment and materials to prevent mixups and contamination. A quarantine area should be set up to separate the incoming drug product, cylinders and vessels, equipment, and the finished product prior to release.

EQUIPMENT CLEANING AND MAINTENANCE
Sections 211.67(a)

All equipment used in the manufacturing of a drug product shall be cleaned, maintained, and sanitized at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality, or purity of the drug.

A word of caution, equipment used to supply industrial product is required to be qualified before it is used with medical products.

If the possibility exists that a medical product, equipment, or containers or closures may

have been exposed to a contaminant(s), then a test for that contaminant(s) is required. The U.S.P. General Notices section states it is impossible to list every possible assay in a U.S.P. monograph.

EQUIPMENT CALIBRATION
Section 211.68

A firm should establish written procedures addressing a calibration schedule for all equipment used during its operations. A firm may reference the manufacturer's instruction manual for the recommended calibration schedule, however, the manual should be available and should be followed to assure proper functioning of all equipment. This is especially true for oxygen analyzers, pressure gauges, vacuum gauges, thermometers, scales, etc.

The current requirement for vacuum gauges is a daily check to assure that the needle returns to zero.

On the other hand, thermometers are required to be calibrated in accordance with the manufacturers recommendation. We have allowed firms to store under lock and key, a thermometer similar to the ones in use in the filling area, and to periodically compare the stored thermometer to the used filling thermometers.

COMPONENTS
Section 211.84(d)(2)

CERTIFICATE OF ANALYSIS (COA) - DRUG PRODUCT

The following information should be provided, at a minimum:

1) Supplier's name and address

2) Name of the Product

3) An Air Liquefaction Statement♦

4) Lot Number or other unique identification number

5) The Actual Analytical results obtained for identity and strength. [Please note that a statement indicating, "Meets the minimum purity of 99.5%, etc. is not acceptable."]

6) Test Method used for analysis. The statements "Meets U.S.P. specifications"

is not acceptable, nor is "Tested via Servomex" since the specific model number is not provided♦

7) Supplier's signature and the date

8) If applicable, the signature of the employee witnessing the testing at the supplier.

♦ If a firm is required to perform full U.S.P. testing, in lieu of receiving a COA with each delivery, a letter provided by the supplier and maintained on file indicating the test method used and/or the air liquefaction statement for all product supplied would be acceptable.

The above information may be provided in different forms, i.e., invoice, cylinder tag, etc., which are required to be maintained on file.

Please note that there are no regulations requiring a supplier to provide a COA. Once the product is delivered or is distributed, the supplier loses control of the product.

SUPPLIER AUDITS

Firms receiving a certificate of analysis or a letter from a supplier are required to perform an audit of any outside supplier in accordance with established written procedures. This may be accomplished by visiting the supplier at least once a year to:

- determine if the supplier is registered with FDA;
- assure the supplier is following appropriate written procedures;
- witness any analytical testing performed, including any calibration procedure; and
- document the audit.

CONTAINER CLOSURES
Sections 211.80 to 94

Drug product containers and closures play a critical role in assuring that the patient is provided a drug product of essentially the same strength, quality, and purity.

The CMG industry is the only industry allowed to reuse the drug product containers and closures. Therefore, high pressure cylinders and all cryogenic vessels are required to

undergo strict prefill inspections, prior to filling with a medical gas.

Prefill Inspections

1. High Pressure Cylinders

Under the GMPs, a firm is required to perform the following inspections on each and every cylinder:

- cylinder markings - The hydrostatic testing date. [Steel cylinders are tested every five (5) years, unless a "*" follows the testing date which means the cylinder may be tested every ten (10) years. Aluminum cylinders must undergo testing every five (5) years.]

  The Department of Transportation has renewed Exemption E-10922 to Ultra Test Corporation, Division of FIBA Leasing authorizing the use of one hundred percent ultrasonic inspection of steel high pressure cylinders in lieu of the internal visual and hydrostatic retest.

- an external examination for dents, arc burns, and other signs of external damage that might cause a cylinder to be unacceptable or unsafe for use. For aluminum cylinders, a visual check of the polyurethane coating or other heat-sensitive indicator, if provided, for evidence of exposure to heat or fire.

- venting or blowing down to atmospheric pressure if any gas is present; or inverted and drained if it contains a liquid.

- during the venting, a "sniff" or odor test is performed to detect the possible presence of a foreign gas. (This test must not be performed on carbon dioxide, nitrous oxide, or anesthetic gases.)

- a hammer test which is a valuable indicator of internal corrosion, should be performed on empty unpressurized cylinders. [This procedure must not be performed on aluminum cylinders.] The hammer test consists of tapping the cylinder sidewall with a light blow using a ball-peen hammer, etc. A good cylinder will make a clear bell-like ring, while a dull ring would indicate internal corrosion. All cylinders with a dull ring should be marked as unacceptable and quarantined.

- the valve assembly should be examined for the presence of debris, oil or grease which should be removed before use, and for the correct CGA valve which is unique for the specific medical gas. Recent problems encountered with valve assemblies has necessitated stricter inspections:

- are the inlet threads or outlet threads damaged?

- is the handwheel or valve stem bent?

- are there noticeable signs of damage?

- are there visible signs of corrosion inside the valve

- are there visible signs of excessive heat or fire damage?

- the correct color for the corresponding medical gas. This inspection along with the significant labeling inspection and the correct CGA valve inspection would provide assurance that the correct medical gas is filled into a cylinder.

- the labeling. Old labels need not be removed if they are identical to the labels currently used, are in good condition and are applicable to the product being filled. However, any labeling containing old lot numbers should be removed.

- evacuation of each cylinder by means of a vacuum pump capable of pulling a vacuum of 25 inches of mercury at sea level before oxygen or any other medical gas is introduced into the filling manifold. [See attached Altitude Pressure chart.] Due to the hazards involved with the old double purging procedure, this procedure is no longer recommended.

Cylinders failing these prefill inspections are required to be quarantined to a separate area to prevent their use in the filling process.

All of the above high pressure prefill inspections are required to be documented on a batch production record under the appropriate headings.

2. Cryogenic home vessels

Cryogenic home vessels are required to undergo certain prefill inspections, prior to filling. The required prefill inspections are usually contained in the manufacturer's manual supplied with each cryogenic vessel. Therefore, at a minimum there should be:

- an external vessel inspection,

- a cryo connection inspection,

- a volume or contents gauge inspection, and

- a label inspection.

Documentation that each cryogenic home vessel has undergone the above inspections

should be entered on a cryogenic home vessel batch production record under the appropriate headings.

3. Large cryogenic vessels

Large cryogenic vessels are required to undergo the same prefill inspections identified above for cryogenic home vessels. In addition, they need to be inspected for DOT markings and the filler must ensure that the pressure relief device on the unit is appropriate for its intended use.

Note: The use of a single entry indicating that all of the above prefill inspections have been performed is not acceptable. A firm should amend its record to provide for an item by item entry, in accordance with Section 211.188(b). [See attached batch production record example for high pressure cylinders for details.]

FILLING OPERATION

The two most common methods of filling high pressure cylinders are:

a) Liquid to Gas. Liquid oxygen is pumped from a storage tank through a vaporizer or heat exchanger converting the liquid into a gas which travels through piping. Attached will be a filling manifold usually with multiple outlets to which the high pressure cylinders are attached to be filled;

b) Gas to Gas, commonly referred to as cascading [See Definition #4]. Gaseous product from a bank of high pressure cylinders such as H, K, Ts, etc. is filled into smaller receiving high pressure cylinders such as D, E, etc.

During the filling operation, the filler is required to perform a heat of compression check which is accomplished by lightly touching the exterior of each cylinder undergoing filling. A warm cylinder indicates the cylinder is filling properly, however, if a cylinder is cool or cold to the touch, the cylinder may not be filling properly and should be investigated and addressed.

Temperature & Pressure

Because of the characteristics of gases in a closed container, such as a high pressure cylinder, to increase in pressure with rising temperature the possibility exists that a cylinder filled at a safe pressure at room temperature could reach a dangerously high pressure at elevated temperatures. Therefore, this increase in the pressure needs to be compensated for to ensure that the cylinder's service pressure is not exceeded.

Since heat and pressure are directly proportional a temperature pressure chart [See attached chart] is used to adjust the filling pressure so that the service pressure will not

be exceeded at 70°F. The filling temperature is determined by attaching a thermometer to the side of one of the cylinders attached to the manifold during filling, including aluminum cylinders. The temperature and filled pressure reading is required to be recorded on the batch production record under the temperature pressure column.

NOTE: The Department of Transportation has a requirement that one cylinder per day per product must be allowed to settle over night and this should be recorded.

If a "+" symbol follows the indicated service pressure stamped on a cylinder's neck, then that cylinder qualifies for a ten percent (10%) overfill unless the valve is equipped with a fusible, metal-backed safety. These are usually found on post valves for gaseous fills only. Aluminum cylinders must not be overfilled.

Valve Leak Testing

During the filling operation, the first of the two required valve leak tests should be performed. At this time, each cylinder valve is tested for valve packing leaks, safety plug leaks and other valve leaks using a leak detecting solution. The valve packing leak test is required to be performed with the cylinder under pressure with the cylinder valve open.

A leak detection solution is sprayed on and around the entire valve assembly. This solution should be oxygen compatible and should not contain hydrocarbons. Solutions containing soap are not recommended since they may be corrosive to the valve stem and may develop a residue buildup.

RETESTING OF CONTAINERS
Section 211.87

Containers and closures are required to be retested for identity, strength, quality, and purity and approved or rejected by the quality control unit, after exposure to conditions that might adversely affect the component, drug product container, or closure.

This would pertain to any container or closure used for industrial products and then later used for medical products. The same would apply to new cryogenic home vessels and any portable units such as walkers or strollers that are used for the first time.

If a cryogenic home vessel is sent out for repair or maintenance then upon return the vessel should be retested for identification at the least, prior to redistribution.

WRITTEN PROCEDURES
Section 211.100(a & b)

There cannot be different standards of quality of drug products for large and small

manufacturers. Written procedures are appropriate regardless of the size or complexity of the operation. Written procedures provide a basis for the uniform performance of a function.

Standard operating procedures are a step-by-step description on performing a task, function, or operation.

Medical gas manufacturers are expected to establish and follow detailed written procedures covering all aspects of their operation. These procedures should cover training, prefill, fill and post fill operations, analytical testing, labeling, calibration and maintenance of the equipment, distribution, recall, complaint files, etc.

In addition, it does little good to enact new procedures and controls if they are not read, understood, and followed by all employees.

CALCULATION OF YIELD
Section 211.103 & 184(c)

On May 11, 1995, the FDA granted the Compressed Gas Association's Citizen Petition (94P-0426/CP 1). Therefore, medical gas manufacturers are exempt from performing the calculation of actual yields and percentages of the theoretical yield as required by Section 211.103, and from the 211.184(c) requirement that records should include an individual inventory record of each component, and a reconciliation of the use of each lot of component.

PACKAGING AND LABELING CONTROL
Sections 211.122, 125, & 130

A firm should establish written labeling procedures covering the receipt, identification, storage, handling and examination of all labeling. Procedures should be established for the reconciliation, issuance, returns, and security of labeling.

There should be written procedures to assure that the correct labeling is used for its drug products, including the identification of each batch of drug product with a lot number.

We are currently working with the CGA on developing labeling guidance, and we anticipate completing a final labeling document this year.

Section 503 of the Food Drug and Cosmetic Act requires prescription drugs to bear the statement: "Caution: Federal law prohibits dispensing without prescription."

However, on September 19, 1996, the agency granted the CGA's petition regarding the

labeling of medical oxygen which is required to contain the statement: "For emergency use only when administered by properly trained personnel for oxygen deficiency and resuscitation. For all other medical applications, Caution: Federal law prohibits dispensing without prescription."

LOT NUMBERS

According to the GMPs, each manifold filling sequence, each uninterrupted filling sequence, each cryogenic vessel filled, and each storage tank following a delivery is considered a new lot and is required to be assigned a new lot number.

The assigning of a single lot number for an entire days production is not acceptable. A manufacturing operation, such as the filling of high pressure cylinders on a multi-outlet manifold, is governed by a set of manufacturing procedures or conditions which when performed from the beginning to the end of a process provides assurance that the batch is uniform and consistent. Further, each batch is in itself a separate entity with little resemblance to the previous batch other than the use of the same incoming materials with subsequent batches exhibiting their own uniqueness.

For firms filling liquid oxygen only for home patient delivery, each of the large cryogenic vessels/dewars placed in a van or a truck are required to be assigned a unique lot number.

At the present time, cryogenic home vessels filled at a patient's home, i.e., curbside, are not required to bear a lot number. However, if a cryogenic home vessel is filled on site and is stored for future delivery, or if a cryogenic home vessel is filled by a third party, then lot numbers are required.

EXPIRATION DATING AND STABILITY TESTING
Sections 211.137 & 166

The Compressed Gas Association submitted a citizens petition to exempt medical gases from compliance with the expiration dating requirements of 21 CFR 211.137. A final decision has not been reached, in the interim, we are not requiring that firms apply expiration dates to the labeling of medical gases.

However, if a firm's written procedures call for an expiration date, then a firm should be following their procedures and apply an expiration date to the product.

HOLDING & DISTRIBUTION
Sections 211.142 & 150

Section 211.142 states written procedures should be established describing the warehousing of the drug product, especially the quarantining of the finished drug product, prior to release.

Section 211.150 states there should be written procedures describing a system by which the distribution of each lot of drug product can be readily recalled.

Please note that reliance on a system of contacting every customer in case of recall is not sound. Under this type of system recalls could be delayed if customers who received recalled products were not contacted because they were not customers at the time of initiation of the recall. Conversely, customers who never received the product could be contacted, thus taxing the resources of the firm and FDA. A blanket recall might also cause unneeded patient anxiety, and the Commissioner does not believe that the same accountability for each lot is inherent in a system that relies on contacting every customer.

LABORATORY CONTROLS
Sections 211.160(a) & 160(b)(4)

Section 211.160(a) - Written procedures covering any specifications, standards, sampling plans, and testing should be established and followed to assure that each batch of drug product conforms to final specifications.

Section 211.160(b)(4) - Oxygen analyzers, instruments, gauges, etc. should be calibrated at suitable intervals in accordance with the manufacturer's instructions.

For the calibration of oxygen analyzers, all gases are required to be calibration standards and should be accompanied by a certificate of analysis certifying the actual test results of the oxygen contents. Calibration standards cannot be medical grade or industrial grade and should be obtained from a manufacture of standard gases. A firm cannot produce its own calibration standards.

COA - Calibration Standards

The following information should be provided:

1) Supplier's name and address

2) Name of the Product (Cannot be medical or industrial grade)

3) Lot Number

4) The Actual Analytical results obtained. A statement indicating, "Meets the minimum purity of 99.8%, etc. may be acceptable as long as the actual results are provided"

5) Supplier's signature and the date

After the filling operations are completed, and the cylinders have been disconnected or removed from the manifold, the second valve leak test should be performed. This test detects any valve outlet leaks. If any leaks are detected, the cylinder should be removed from service and quarantined until repairs can made.

TESTING AND RELEASE
Sections 211.165(a) & 165(e)

The most frequently encountered GMP problem is inadequate assurance of the quality of the incoming and/or the finished product. The testing requirement for cylinders filled on a multiple outlet manifold is one filled cylinder from each manifold filling sequence should be assayed for identity and strength, either by 1) the U.S.P. test procedure or 2) a test procedure capable of producing equivalent or greater than U.S.P. test results.

For cylinders filled individually, i.e., one at a time, then one filled cylinder per uninterrupted filling sequence should be tested for identity and strength. An uninterrupted filling sequence is a single, continuous filling sequence with no breaks or shut-downs occurring during the filling provided the same personnel, equipment, and lot of component are used. If the filling sequence is interrupted then additional testing is required. This procedure pertains to high pressure cylinders that are filled individually, i.e., one at a time, not cryogenic vessels.

At the current time, for the testing of nitrogen a facility may use an oxygen analyzer to test for the absence of oxygen and subtract this result from 100% to determine the nitrogen content provided all of the following conditions are met:

1) the supplier of the incoming nitrogen is registered with FDA,

2) a valid certificate of analysis is received with each delivery of nitrogen,

3) the filling system has dedicated lines, and these supply lines are traceable from the bulk source to the filling manifold. If there exists a possibility that another gas, other than oxygen, whether it be industrial or medical, could be introduced and contaminate the product, then full U.S.P. testing would be required. For blending, i.e., medical air, finished product testing for the active ingredient, i.e., oxygen is required, and

4) the firm performs a supplier audit (See above for specific requirements).

What is the official method as outlined in the United States Pharmacopeia (U.S.P.) 23.

U.S.P. Oxygen Monograph

The U.S.P. Oxygen monograph lists the potency as being not less than 99.0% by volume of O_2. It also states that oxygen produced by the air liquefaction process is exempt from the requirements of the test for Carbon dioxide and Carbon monoxide.

Note: If a firm fills Oxygen U.S.P. and fails to have on file documentation that the oxygen it receives is produced by the air liquefaction process, then a firm is required to perform the identity, strength, carbon dioxide and carbon monoxide tests, not just an identity and strength test. This documentation may be in the form of a certificate of analysis or a letter from the supplier.

The official method which is commonly referred to as the "ORSAT" buret method utilizes a calibrated 100 ml buret, copper wire, and ammonium chloride and ammonium hydroxide solutions which are mixed together and equilibrated by agitation. A 100.0 ml sample of the gas is drawn into the buret and agitated, the residual gas is then measured.

In addition, a specific identity test is required to be performed at the same time, since carbon dioxide is capable of giving similar results. This is usually accomplished by using either a carbon dioxide detector tube or a properly calibrated handheld oxygen analyzer.

The accuracy of the U.S.P. procedure is $\pm$0.1%.

LIQUID PHASE

Because the pressure in a closed vessel containing carbon dioxide and nitrous oxide will increase with a rise in temperature, the possibility always exists that a cylinder charged at a safe pressure at normal temperatures might reach a dangerously high pressure at high ambient temperatures. Therefore, nitrous oxide and carbon dioxide are filled individually on a scale, as liquids where pressure does not indicate the amount filled. These cylinders are filled individually by weight which should not exceed 68% of the weight of water the cylinder will hold at 60°F (15.6°C).

One cylinder filled during an uninterrupted filling sequence should be tested for identity and strength, prior to release.

If a firm is utilizing the Pressure Differential method to assay nitrous oxide, please beware that an identity test is required to be performed concurrently, since carbon dioxide and nitrous oxide can mix. The pressure differential method has been evaluated and found to be an acceptable alternative testing methodology.

GAS MIXTURES

If the product is a mixture of two gases, then every cylinder should be tested for the identity and strength of one of the gases, usually the active ingredient. In addition, an identity test for the other gas should be performed on one cylinder from the manifold filling sequence.

For a mixture containing three gases, every cylinder should be tested for the identity and strength of two of the gases, and one cylinder from each manifold filling sequence should be tested for the identity of the third gas.

Alternative Analytical Equipment

If an alternate method is to be used for the analysis of medical gases, then the accuracy, sensitivity, and reproducibility of the method is required to be established and documented.

Analyzers we have seen that operate on the paramagnetic susceptibility principle may have equivalent U.S.P. accuracy, however, you cannot assume that all similar analyzers do. You should check the manufacturer's operating/instruction manual to determine the accuracy of an oxygen analyzer.

For paramagnetic analyzers with the required accuracy, as long as a firm has the manufacturer's operation manual on file, and the analyzer is calibrated according to the manufacturer's procedure then this will suffice as documentation of U.S.P. equivalency. However, if a firm does not have the manufacturer's operating manual, then the firm's own study is required.

NOTE: A letter merely stating U.S.P. equivalency would not be acceptable, unless supported by the manufacturer’s validation documentation and this study should be maintained on file.

On the other hand, properly calibrated oxygen analyzers operating on the fuel, electrochemical, galvanic, or polarographic cell principle will provide a specific oxygen identification test result only. At the present time, we are unaware of any of these instruments that have the accuracy required to provide an equivalent Oxygen U.S.P. strength result. Typically, these analyzers have an accuracy of $\pm$ 1 to 3%, not the required $\pm$0.1%.

RECORDS & REPORTS
Section 211.180(a) & 182

Any record required by the GMPs should be maintained in compliance with this part.

Record retention requirements:

1) if an expiration date is used, then all records should be retained for at least one (1) year after the expiration date of the batch.

2) if no expiration date is used, then records are to be retained for at least 3 years after distribution of the batch.

Records may be in the form of true copies or electronic copies. Records covering equipment cleaning and/or maintenance should be established. For the filling of cryogenic home vessels, there should be a separate log documenting when a vessel is sent out for maintenance or repair.

MASTER PRODUCTION AND CONTROL RECORDS
Section 211.186

While master production and control records are required, this requirement may be met by establishing a manual containing all written procedures, a specimen of the labeling, the date and signature of the individual responsible for the preparation of all required records, and the signature of a second person who independently checked and dated these records.

BATCH PRODUCTION AND CONTROL RECORDS
Section 211.188

Batch production records should document all significant steps performed during the filling operations, such as the prefill inspections for the high pressure cylinders and cryogenic vessels, the number and size cylinders filled, the filling inspections, the post fill checks, analytical test results, the lot number assigned, the final temperature and pressure results, labeling accountability, i.e., issued, applied, returned, damaged, etc., the initials of the pumper/analyst, the signature of the individual who checked the entries for accuracy and completeness, the dates the above procedures were performed, etc.

It is unacceptable for a firm to use a single entry to indicate that all of the significant steps have been performed. A firm should amend its batch production record to provide for an item by item entry. [See the attached batch production record example for high pressure cylinder filling for details.]

A batch production record is a control record documenting that all of the required operations were performed during a comprehensive or elaborate manufacturing procedure or process. In fact, a batch production record is a snapshot of the actual production at the time of its performance.

LABORATORY RECORDS
Section 211.194

Laboratory records should include complete data from all tests necessary to assure compliance with established specifications and standards. This would include all graphs, charts, etc., all calculations performed in connection with a test especially for mixtures or

blends, the initials or signature of the analyst, and the initials or signature of a second individual showing that the original records have been reviewed and are in compliance with all established standards.

DISTRIBUTION RECORDS
Section 211.196

Records should contain the name and strength of the product, what the patient received, i.e., D, E cylinders, cryogenic home vessel, the name and address of the consignee, customer, or patient, and the date and quantity shipped.

COMPLAINT FILES
Section 211.198

Written procedures should be established and followed describing the handling of all written and oral complaints, a detailed written record of each complaint, and the conclusion of any investigation of that complaint.

DRUG PRODUCT SALVAGING
Section 211.208

Products failing to meet U.S.P. specifications are required to be vented. Repeated testing, in order to pass a drug product is not allowed, unless a thorough investigation is performed, completed and documented.

ADAPTERS

The use of adapters to circumvent the specific CGA valves associated with a specific medical gas is not only illegal but also a very dangerous practice. There have been mixups and contamination that have occurred in the past due to the use of adapters.

For the filling of mixtures, adapters may be used, however, written procedures detailing a system of checks should be in place to prevent mixups or contamination, and these should be documented. The adapters are required to be under security with limited access.

COMPUTER SYSTEMS

Before a firm decides to convert any of its manual operations to an automated operation that will be controlled by a computer system and associated software, it is required to validate the computer system and associated software.

What exactly is validation? Well, according to the Guideline on General Principles of Process Validation, May 1987, validation is defined as establishing documented evidence which provides a high degree of assurance a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

What are the possible consequences of not complying with the GMPs?

How many times have you heard the statement, "What could go wrong with my oxygen? I buy it from a reputable source! I know what I'm doing! I fill oxygen only!"

Well, manufacturers report that each year there are returned to them supposedly empty cylinders that contain either a gas other than that originally shipped or a foreign odor. Some of these contaminating gases may be flammable, and intermixing a flammable and an oxidizing gas may cause a serious explosion.

On May 24, 1983, a large welding supply company in the southeast, delivered and connected a VGL thought to contain medical oxygen to a local hospital. During the course of the evening, the product was administered to a premature infant, a 46 year old male, and a 27 year old female in three different areas of the hospital and all three died. Analysis of the gas found that the alleged oxygen was in fact argon. To further complicate matters, the VGL was partial labeled "Liquid O" and had a second label on the other side which read argon, and the fill line had an argon fitting while the discharge line had an oxygen fitting.

In 1987, a large welding supply company located in the northeast, jury-rigged four oxygen cylinders and placed CO_2 into these cylinders which were not painted the appropriate color for oxygen. However, the cylinders were correctly labeled as Oxygen U.S.P. and had the correct CGA 540 oxygen valve.

In addition, the firm failed to have written procedures covering the filling and handling of different colored cylinders. Four (4) of the cylinders were subsequently sent to a hospital and administered to two patients undergoing surgery. One patient's death was attributed to carbon dioxide exposure while the other patient was seriously injured.

On December 20, 1993, a home care company located in the northeast and filling liquid oxygen only, had it's employee go to their supplier to pick up a GP-45 of Oxygen U.S.P. The supplier's employees were very busy and were unable to accompany the home care company’s employee to the loading dock, so they authorized the employee to go to the loading dock and select one of the GP-45s. Unfortunately, the employee who was inadequately trained, selected a GP-45 of argon, not Oxygen U.S.P. Although a certificate of analysis was provided, no testing was performed and the labeling was not examined.

The employee loaded the vessel onto the van and went to three (3) patients homes to fill their vessels, however, the employee encountered one little problem. When he went to fill the cryogenic home vessels, the discharge line was not compatible with the vessels fittings.

So he took a fitting from a spare oxygen vessel and installed it on the GP-45, he could now fill the patients cryogenic vessels with the deadly product. Luckily, the next day, the employee became aware of the argon mixup and retrieved all 3 vessels with no injuries. Fortunately, these three patients were not dependent on high inspired oxygen concentrations.

In March 1996, I received a report of several deaths associated with contaminated oxygen occurring at a VA hospital in the southwest. According to the report, a large storage tank was being replaced, and a temporary 500 gallon cryogenic vessel was brought in and connected to the hospitals main oxygen system via a 50 foot hose. Analysis of the 50 foot hose tested positive for the presence of trichloroethylene, a standard cleaning chemical.

On July 15, 1996, in Fredericksburg, Virginia, the former president of a medical oxygen facility pleaded guilty to making false statements to the Food and Drug Administration about his company's testing and filling of medical oxygen. During the February inspection, the president was informed of significant GMP violations occurring at the firm. In March, he agreed to recall the adulterated drug product and informed FDA that he had done so. However, FDA later discovered that the firm in fact did not recall the adulterated product. The president was sentenced to serve one year and one day in prison, to perform 200 hours of community service, and to pay a $30,000 fine for making false statements to FDA.

What's on the horizon for medical gases:

*a new agency guidance document which will resemble Fresh Air 97;

*final decisions on the CGA citizen petition regarding expiration dating and stability studies;

*final labeling guidance for all medical gases; and

*a new policy for emergency medical services (EMS), i.e., fire departments, ambulance services, rescue squads, medivac, etc. who fill cylinders for their own use.